SP - 23

Rancho Group.

ZPATG	TRTG
01011	0
01012	0
01017	0
01024	0
01025	0
01031	0
01049	0
01060	0
01074	0
01083	0
01105	0
01106	0
01112	0
01114	0
01130	0
01132	0
01142	0
01143	0
01150	0
01154	0
01164	0
01209	0
01258	0
01260	0
01261	0
01263	0
02005	0
02023	0
02053	0

Total: 29 pts

54 pts

8/2/01

qry_ALLCOMPLICAT

Placebo Group

Total 54pts (SP - 50)

Sponsor data - 50 patients

ZPATG	TRTGP
01006	0
01011	0
01012	0
01018	0
01025	0
01029	0
01060	0
01062	0
01068	0
01076	0
01086	0
01094	0
01105	0
01106	0
01109	0
01112	0
01113	0
01130	0
01137	0
01140	0
01142	0
01146	0
01149	0
01150	0
01189	0
01192	0
01206	0
01215	0
01219	0
01225	0
01233	0
01245	0
01250	0
01258	0
01261	0
01263	0
01265	0
01267	0
01269	0
01273	0
01281	0
02005	0
02013	0
02021	0
02023	0
02028	0
02045	0
02048	0

Total. 54 patients

ZPATC	TRTG
02050	0
02053	0
02057	0
02062	0
02064	0
02069	0

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise M. Peltier	From: Debbie Vause for Paul Zimmerman
Fax: 410-631-6338	Fax: 301-594-0499
Phone: 410-631-6356	Phone: 301-594-5724
Pages, including cover sheet: 11	Date: August 13, 2001
Re: NDA 20-637 / Gliadel Wafer	

☐ Urgent ☑ For Review ☐ Please Comment ☑ Please Reply ☐ Please Recycle

● Dear Ms. Peltier:

Please review the attached questions and provide a response as soon as possible. Also, please telephone me today with a time frame of when to expect your responses.

Thank you,

Debbie Vause

Sent 8/13/01
Ved into dfs 8/14/01 N → CSO → Zimmerman → NDA 20 637 fax.

Thank you for sending the clarification of the histological diagnoses in the category "other".

In addition we have the following questions:

1. Please explain the differences between the number of patients with the histological diagnosis of anaplastic oligoastrocytoma in the placebo group in Table 7: Tumor Characteristics – Histological Type. Two patients are listed in this category, however in the data base (UPAT, R_DIAGH), 4 patients are listed. Patient ID numbers are as follow: **02013; 01114; 01164; 02064.**

2. Please resolve the discrepancies between the data on the number of patients in both groups who received anticonvulsants and steroids. A list of patient ID numbers with the corresponding medication is attached. Each patient was counted only once.

3. Please provide the patient ID numbers for the AE listed as "Intracranial Hypertension". Sponsors data differs in three tables from the Final Study report:
   p.94 – Table 46: Gliadel – 11 patients, placebo – 2 patients;
   p.96 – Table 47: Gliadel – 10 patients, placebo – 2 patients;
   p.107 – Table 56: Gliadel – 7 patients, placebo – 2 patients.

We found 8 and 3 patients with intracranial hypertension in the Gliadel and placebo arm, respectively.

3. Please explain how the "Number of Wafer Intended to be Implanted" was determined by the surgeon (Append. F, Table 3.01).

GROUP	ZPATCODE	LIMND
0	01011	TEGRETOL
0	01012	TEGRETOL
0	01017	TEGRETOL
0	01018	TEGRETOL
0	01024	PHENYTOIN
0	01036	TEGRETOL
0	01062	TEGRETOL
0	01074	TEGRETOL
0	01083	PHENOBARBI
0	01094	PHENYTOIN
0	01112	TEGRETOL
0	01113	TEGRETOL
0	01130	TEGRETOL
[redacted]		[redacted]
0	01145	PHENYTOIN
0	01146	PHENYTOIN
0	01153	TEGRETOL
0	01154	TEGRETOL
0	01160	TEGRETOL
0	01189	PHENYTOIN
0	01192	PHENYTOIN
0	01193	TEGRETOL
0	01194	TEGRETOL
0	01206	PHENYTOIN
0	01210	TEGRETOL
0	01215	TEGRETOL
0	01228	PHENYTOIN
0	01229	TEGRETOL
0	01245	PHENYTOIN
0	01249	TEGRETOL
0	01250	TEGRETOL
0	01261	TEGRETOL
0	01265	LORAZEPAM
[redacted]		[redacted]
0	01267	PHENYTOIN
0	01269	TEGRETOL
0	01270	TEGRETOL
0	01281	LORAZEPAM
0	02005	PHENYTOIN
[redacted]		[redacted]
0	02021	TEGRETOL
0	02023	TEGRETOL
0	02026	LORAZEPAM
0	02028	TEGRETOL
0	02045	TEGRETOL
[redacted]		[redacted]
0	02048	TEGRETOL
0	02050	LORAZEPAM

Patients who received anticonvulsants:

Sponsor: Placebo: 5 pts (10%)
Gliadel: 12 pts (24.5%)

Reviewer: Placebo: 5/patients (42.5
Gliadel: 28 pts (23.3%)

GROUP	ZPATCODE	LIMND
0	02050	PHENYTOIN
0	02053	PHENYTOIN
0	02057	PHENYTOIN
0	02064	TEGRETOL
0	02069	LORAZEPAM
[redacted]		
1	01014	TEGRETOL
1	01019	TEGRETOL
1	01020	TEGRETOL
1	01030	TEGRETOL
1	01051	TEGRETOL
1	01059	TEGRETOL
1	01063	TEGRETOL
1	01066	TEGRETOL
1	01069	TEGRETOL
1	01073	TEGRETOL
1	01075	TEGRETOL
1	01091	TEGRETOL
1	01115	TEGRETOL
1	01129	TEGRETOL
1	01131	TEGRETOL
1	01141	TEGRETOL
1	01144	TEGRETOL
1	01151	TEGRETOL
1	01152	TEGRETOL
1	01158	TEGRETOL
1	01159	TEGRETOL
1	01167	TEGRETOL
1	01173	PHENOBARBI
1	01196	TEGRETOL
1	01301	TEGRETOL
1	02029	TEGRETOL
1	02046	LORAZEPAM
1	02061	TEGRETOL

GROUP	PTS
1	01005
1	01007
1	01009
1	01010
1	01013
1	01014
1	01019
1	01020
1	01021
1	01022
1	01028
1	01030
1	01032
1	01033
1	01034
1	01050
1	01051
1	01054
1	01056
1	01057
1	01059
1	01061
1	01063
1	01065
1	01066
1	01069
1	01070
1	01073
1	01075
1	01079
1	01080
1	01082
1	01084
1	01085
1	01087
1	01090
1	01091
1	01093
1	01095
1	01107
1	01110
1	01111
1	01115
1	01116
1	01122
1	01129
1	01131
1	01133

Pts who received KS

Total - 114 (95%)

(Group 1)

p. 66, FSR: 29 pts (59.2%)

(Continued: Patients who received steroids - Group 1")

GR	PATIENTID
1	01135
1	01138
1	01139
1	01141
1	01144
1	01147
1	01148
1	01151
1	01152
1	01158
1	01159
1	01161
1	01162
1	01167
1	01170
1	01172
1	01173
1	01181
1	01182
1	01190
1	01191
1	01196
1	01197
1	01201
1	01205
1	01207
1	01211
1	01212
1	01213
1	01216
1	01217
1	01218
1	01226
1	01227
1	01235
1	01236
1	01256
1	01257
1	01259
1	01262
1	01264
1	01266
1	01268
1	01271
1	01272
1	01274
1	01277
1	01282

(Continued: Patients who received steroids - Group "1")

GROUP	P
1	01284
1	01292
1	01293
1	01297
1	01301
1	01305
1	02006
1	02022
1	02024
1	02046
1	02047
1	02049
1	02052
1	02054
1	02058
1	02059
1	02061
1	02063

Pts who received steroids

Total - 117 (98%)

f. 66, FSR: 30 pts (60%)

GR[illegible] ZIP [illegible]
001006
001008
001011
001012
001015
001016
001017
001018
001023
001024
001025
001027
001029
001031
001035
001036
001049
001052
001053
001055
001058
001060
001062
001067
001068
001074
001076
001077
001078
001081
001083
001086
001088
001089
001092
001094
001105
001106
001109
001112
001113
001114
001130
001132
001134
001136
001137
001140

(Continued – Patients who received steroids)
Group 0

GROUP	PATIENT
0	01142
0	01143
0	01145
0	01146
0	01149
0	01150
0	01153
0	01154
0	01157
0	01160
0	01163
0	01164
0	01165
0	01169
0	01171
0	01177
0	01178
0	01183
0	01184
0	01189
0	01192
0	01193
0	01194
0	01206
0	01208
0	01209
0	01210
0	01214
0	01215
0	01219
0	01220
0	01225
0	01228
0	01229
0	01233
0	01234
0	01245
0	01246
0	01249
0	01250
0	01258
0	01260
0	01261
0	01263
0	01265
0	01267
0	01269
0	01270

(continued – patients who received steroids)
Group "0"

GROUP	ID
0	01273
0	01281
0	01283
0	01289
0	01309
0	02005
0	02021
0	02023
0	02026
0	02028
0	02045
0	02048
0	02050
0	02051
0	02053
0	02055
0	02057
0	02060
0	02062
0	02064
0	02069

SUMMARY OF PATIENTS WITH
CONCOMITANT CORTICOSTEROIDS
OR ANTICONVULSANTS
OVERALL AND BY HISTOLOGICAL SUBTYPE
AND TREATMENT GROUP

Overall

	Treatment Group		
	Polifeprosan / Carmustine (N=120)	Placebo (N=120)	ALL (N=240)
Number of Patients			
Without Concomitant Therapy	71 (59.2%)	70 (58.3%)	141 (58.8%)
With Concomitant Therapy	49 (40.8%)	50 (41.7%)	99 (41.3%)
Concomitant Medication By Therapeutic Class			
Corticosteroid (Systemic)			
Yes	29 (59.2%)	30 (60.0%)	59 (59.6%)
Anticonvulsants			
Total	12 (24.5%)	5 (10.0%)	17 (17.2%)

Table : 1.09

Confirmation Report – Memory Send

Page : 001
Date & Time: Aug-13-01 11:27am
Line 1 : 3015940499
Machine ID : FDA - Division of Oncology Drug Products

Job number	:	275
Date	:	Aug-13 11:24am
To	:	☎914106316338
Number of pages	:	011
Start time	:	Aug-13 11:24am
End time	:	Aug-13 11:27am
Pages sent	:	011
Status	:	OK

Job number : 275 *** SEND SUCCESSFUL ***

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise M. Peltier	From: Debbie Vause for Paul Zimmerman
Fax: 410-631-6338	Fax: 301-594-0499
Phone: 410-631-6356	Phone: 301-594-5724
Pages, including cover sheet: 11	Date: August 13, 2001
Re: NDA 20-637 / Gliadel Wafer	

☐ Urgent ☒ For Review ☐ Please Comment ☒ Please Reply ☐ Please Recycle

● Dear Ms. Peltier:

Please review the attached questions and provide a response as soon as possible. Also, please telephone me today with a time frame of when to expect your responses.

Thank you,

Debbie Vause

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise Peltier	From: Debbie Vause for P. Zimmerman
Fax: 410-631-6884	Fax: 301-594-0499
Phone: 410-631-6300	Phone: 301-594-5724
Pages, including cover sheet: 1	Date: August 14, 2001

Re: NDA 20-637 / Gliadel Wafer / Facsimile date 8/2/01 & Transmission Sheet Date 8/3/01

☐ Urgent ☒ For Review ☒ Please Comment ☐ Please Reply ☐ Please Recycle

● Dear Ms. Peltier:

In the facsimile submission dated 8-2-01 regarding randomization, you stated "The randomization algorithm was accomplished with each center in a given country." Was the randomization stratified by CENTER or COUNTRY?

In the same facsimile you also stated "...using a randomization code (block size of four) independently of randomization code of any other study center. Does this mean that a specific block only be used by a center? Please clarify this statement.

Please review the attached questions and provide a response by COB on Wednesday, August 15, 2001.

Thank you,

Debbie Vause

sent 8/14/01
/ed into dfs 8/14/01

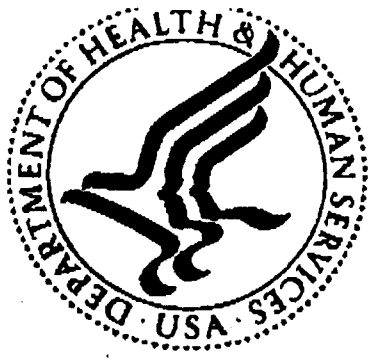
MESSAGE CONFIRMATION

08/14/01 12:29

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
08/14	00'30"	410 631 6884	CALLING	01	OK	0000

08/14/01 12:28 NO.125 P01

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise Peltier	From: Debbie Vause for P. Zimmerman
Fax: 410-631-6884	Fax: 301-594-0499
Phone: 410-631-6300	Phone: 301-594-5724
Pages, including cover sheet: 1	Date: August 14, 2001

Re: NDA 20-637 / Gliadel Wafer / Facsimile date 8/2/01 & Transmission Sheet Date 8/3/01

☐ Urgent ☒ For Review ☒ Please Comment ☐ Please Reply ☐ Please Recycle

Dear Ms. Peltier:

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 6

Date: August 22, 2001

COMMENTS: The attached concern NDA 20-637/S-016.

1. Please explain the differences between number of patients with brain edema in both treatment groups. We found 36 patients with brain edema in the Gliadel group (Sponsor's data is 27 patients), and 29 patients in the placebo group (Sponsor's data is 27 patients). Each patient was counted only once. A list of patient ID numbers is attached.

2. Please clarify the number of patients in the intent to treat population who did not receive radiation therapy: the total FDA count is 15 patients in the Gliadel group and 12 patients in the placebo group. This differs from the number of patients presented by the Sponsor in Table 20 (11 and 9 patients or the Gliadel and placebo group, respectively). A list of patient ID numbers who did not have radiation starting date is attached.

3. We agree with the Sponsor's data on the number of patients (17) in the Gliadel group who received additional chemotherapy. However, the number of patients who received chemotherapy in the placebo group is by our account 17 as well (Sponsor's data is 12 patients). Please resolve the discrepancy. A list of patient ID numbers in the placebo group who did receive chemotherapy is attached.

4. Please clarify what was done during the implantation when it was discovered that wafers had been broken in more than 2 pieces. Were additional packages with wafers available at that time?

ZPATCODE	TRTGR	GROUP	DERAND	DERADSI	RD_RADSR
01007	1	1	1/3/98		
01008	0	0	2/25/98		
01014	1	1	6/1/98		
01057	1	1	8/7/98		
01074	0	0	7/10/98		
01090	1	1	6/18/98		
01092	0	0	10/12/98		
01121	1	1	7/2/98		
01123	0	0	12/21/98		
01142	0	0	10/22/98		
01170	1	1	11/18/98		
01181	1	1	12/16/98		
01189	0	0	1/11/99		
01193	0	0	11/26/98		
01205	1	1	1/27/99		
01207	1	1	2/11/99		
01209	0	0	12/18/98		
01212	1	1	2/3/99		
01245	0	0	3/15/99		
01268	1	1	6/14/99		
01293	1	1	4/28/99		
02026	0	0	8/13/98		
02057	0	0	3/18/99		
02058	1	1	4/22/99		
02059	1	1	5/5/99		
02060	0	0	4/30/99		
02063	1	1	6/21/99		

Patients who received Chemotherapy

Chemo Census 8/21/01

TRTGRP	ZPATCODE
0	01011
0	01012
0	01015
0	01068
0	01124
0	01140
0	01146
0	01164
0	01250
0	01263
0	01273
0	02013
0	02021
0	02028
0	02048
0	02053
0	02064
1	01013
1	01014
1	01028
1	01050
1	01181
1	01207
1	01259
1	01262
1	01264
1	01275
1	01292
1	02014
1	02022
1	02029
1	02046
1	02047
1	02061

Brain Edema

qry_ALLCOMPLICAT

8/2/01

Sponsor: 27

Hiadel Group.

ZPATC	TRTG
01005	1
01007	1
01009	1
01010	1
01014	1
01020	1
01028	1
01032	1
01033	1
01050	1
01056	1
01061	1
01063	1
01069	1
01070	1
01087	1
01093	1
01107	1
01111	1
01116	1
01122	1
01133	1
01138	1
01141	1
01144	1
01151	1
01152	1
01205	1
01268	1
01271	1
01272	1
01297	1
02006	1
02014	1
02054	1
02059	1

- d. 1; 84

Total: 36 pts

Sponsor data - 27 patients

qry_ALLCOMPLICAT

8/2/01

SP - 23

Placebo Group.

ZPATC	TRTG
01011	0
01012	0
01017	0
01024	0
01025	0
01031	0
01049	0
01060	0
01074	0
01083	0
01105	0
01106	0
01112	0
01114	0
01130	0
01132	0
01142	0
01143	0
01150	0
01154	0
01164	0
01209	0
01258	0
01260	0
01261	0
01263	0
02005	0
02023	0
02053	0

Total: 29 pts

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 6

Date: August 22, 2001

COMMENTS: The attached concern NDA 20-637/S-016.

08/22/01 14:51 FDA-DODP → 9141063168884 NO.010 D01

MESSAGE CONFIRMATION

08/22/01 14:54
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
08/22	01'36"	410 631 6884	CALLING	06	OK 0000

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Louise Peltier, Guilford
Fax: 410 631-6884

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 10-19-01

COMMENTS: Re: your pending NDA 20-627/S016 (Gliadel), please see attached request from medical officer.

Thanks
Dotti for Paul Zimmerman

Please provide information on identification of pathogens for patients who developed brain abscesses/wound infections on Study T-301. Patients ID numbers as follow:

Gliadel group:
01005
01020
01063
01085
01201
01275
02024
02059

Placebo group:
01137
01036
01077
01083
01149
01177
02021
02023
01020

...to the above address by mail. Thank you.

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Louise Peltier, Guilford
Fax: 410 631-6884

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 10-19-01

COMMENTS: Re: your pending NDA 20-627/S016 (Gliadel), please see attached request from medical officer.

Thanks
Dotti for Paul Zimmerman

10/19/01 13:15 NO.171 P01

MESSAGE CONFIRMATION

10/19/01 13:17

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
10/19	00'46"	410 631 6884	CALLING	02	OK 0000

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: October 24, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please clarify which primary brain tumor classification system is employed for categorizing tumor histology in the Study T-301.

...and return it to us at the above address by mail. Thank you.

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: October 24, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please clarify which primary brain tumor classification system is employed for categorizing tumor histology in the Study T-301.

10/24/01 14:02 FDA-DDDP → 9141063168884 NO.025 D01

10/24 00'28" 410 631 6884 CALLING 01 - OK 0000

DATE S.R-TIME DISTANT STATION ID MODE PAGES RESULT

10/24/01 14:03
ID=FDA-DDDP

MESSAGE CONFIRMATION

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: November 26, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please provide the exact histological diagnosis for the patient ID 02013 from the placebo group. This patient listed as "other" in the Sponsor FAX letter on August 15, anaplastic oligoastrocytoma in the electronic dataset (referee pathologist), and as anaplastic oligodendroglioma in the Appendix IV.A. Patient data listing.

...at the above address by mail. Thank you.

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: November 26, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please provide the exact histological diagnosis for the patient ID 02013 from the placebo group. This patient listed as "other" in the Sponsor FAX letter on August 15, anaplastic oligoastrocytoma in the electronic dataset (referee pathologist), and as anaplastic oligodendroglioma in the Appendix IV.A. Patient data listing.

11/26/01 13:24 FDA-DDDP → 9141063168884 NO.065 D01

MESSAGE CONFIRMATION

11/26/01 13:25
ID=FDA-DDDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
11/26	00'29"	410 631 6884	CALLING	01	OK 0000

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: November 26, 2001

COMMENTS: The attached concern NDA 20-637/S-016.

Please explain the differences in the histological tumor characteristics listed in Table 13, p. 59 of Final Study Report and Table 6, p.14 of the Briefing Document.

please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: November 26, 2001

COMMENTS: The attached concern NDA 20-637/S-016.

Please explain the differences in the histological tumor characteristics listed in Table 13, p. 59 of Final Study Report and Table 6, p.14 of the Briefing Document.

11/26/01 12:51 FDA-DODP → 9141063168B4 NO.064 D01

MESSAGE CONFIRMATION

11/26/01 12:52
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
11/26	00'29"	410 631 6884	CALLING	01	OK 0000

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HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: November 30, 2001

COMMENTS: The attached concern NDA 20-637/S-016.

Please provide all ID numbers for patients with the following histological diagnoses:

Anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and "other" (except for # 02013).

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DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 3

Date: December 3, 2001

COMMENTS: The following concern NDA 20-637/S-016.

1. Please clarify what radiation therapy regimens were given to the following patients:

"Standard and non-standard" category, **GLIADEL group:**

ID 01069: in the database patient has 2 records (standard and non-standard with the same dates). CRF – standard;

ID 02022: in the database patient has 2 records. CRF – standard;

ID 01107: in the database patient has 2 records (standard and non-standard with the same dates). CRF – unclear, since neither box for "Standard" or "non-standard" has been checked and no comments provided.

<u>"Standard and non-standard" category, **placebo group:**</u>

ID 01011: in the database patient has 2 records (standard and non-standard. CRF – standard;

01105: in the database patient has 2 records (standard and non-standard with the same dates). CRF – standard;

01068: in the database patient has 2 records (standard and non-standard with the same dates). CRF – standard;

01261: in the database patient has 2 records (standard and non-standard). CRF - Non-standard;

02023: in the database patient has 2 records (standard and non-standard). CRF- standard.

APPEARS THIS WAY
ON ORIGINAL

The following patients who were listed as "No radiation therapy" category in the database, included into different categories in the CRF. Please explain.

GLIADEL group:

In the **CRF** patients **ID 01170; 01293; 01014; 01181 and 02058** listed as "non-standard".

ID 01057 listed as "standard".

ID 01007; 01090; 01268; 02059; 02063 – unclear, since neither box for "Standard" or "non-standard" has been checked and no comments provided.

ID 01121; 01205; 01207; 01212 do not have CR/6 page in their CRF.

Placebo group:

ID 01142; 01189; 01209 listed as "non-standard".

ID 01123 listed as "standard".

ID 01008; 01092; 01193; 02026; 02057; 02060 – unclear, since neither box for "Standard" or "non-standard" has been checked and no comments provided.

ID 01295 does not have CR/6 page in their CRF.

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HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: December 5, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please clarify whether a central, local, or referee neuropathologist determined the final histological diagnosis for "non-GBM" patients who had discrepant findings between local and central pathologists?

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DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: December 5, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Your FAX dated and sent 12/3 provided ID numbers for patients with the histological diagnosis of anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma and other (i.e. all patients who would fall into the category of non-GBM excluding metastatic disease). The numbers of patients with these diagnoses are not the same as submitted in the NDA and no source documentation has been provided to allow our verification. The electronic database differs from your 12/3 submission.

Please provide the source documentation.

Also, are source documents for refereed and final pathology somewhere in the CRF? If so, please identify where.

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DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 21

Date: January 30, 2003

COMMENTS: The following concern NDA 20-637/S-016.

(This fax included FDA revise pi of 20 pages which is not included here.)

Changes made in the GLIADEL label.

1. Section Adverse Reactions p.10 "GLIADEL wafer was not reported to be cause of death in any of the GLIADEL wafer clinical trials" was deleted.

Reason: There was a total of 7 deaths (5 in the GLIADEL and 2 in placebo group) in the first 30 Days of Randomization (initial surgery). Conventionally death in the first 30 days of treatment is attributed to the study drug.

2. Section Adverse Reactions p.10 "The spectrum of adverse events observed in patients who received GLIADEL wafer or placebo in clinical studies was consistent with that encountered in patients undergoing craniotomy for malignant gliomas" was deleted.

Reason: There was no third arm in this trial where patients with newly diagnosed malignant gliomas received only surgical treatment followed by radiation. Therefore, the incidence of adverse events described in patients in the GLIADEL and placebo groups with adverse events in patients undergoing craniotomy for malignant gliomas can not be compared.

3. Section Seizures, p.14 "The occurrence of seizures did not reduce the survival benefit of GLIADEL wafer" was deleted.

Reason: The treatment effect (survival) of GLIADEL wafer on a subgroup of patients with seizure was not performed.

4. On pages 3 and 4 p-value numbers were changed to "p-value <0.05."

Reason: The exact value of p-value is uncertain because of multiple comparisons.

5. On page 6, You must round the p-value to two decimal places, i.e., p = 0.01.

6. Please reorder the AE tables by AE category from highest to lowest frequency so the labeling is consistent with CFR 201.57 (g) (2).

7. On page 8, INDICATION has been slightly modified.

8. The following sentence has been add after the ADVERSE REATIONS title:

Adverse reactions for the trials are described in the tables below.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
2/6/03 09:07:05 AM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: August 19, 2002

COMMENTS:

Regarding your NDA 20-637 communication dated August 5, 2002 (received August 16, 2002) we have the following comment:

FDA agrees with Guilford's proposed plan for the data collection and analysis cut off.

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/s/

Paul Zimmerman
8/19/02 03:31:09 PM
CSO

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DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 2

Date: June 25, 2002

COMMENTS: The attached concern your NDA 20-637 June 7, 2002 communication.

Regarding collection of additional data -- (1) we will want to know if patients had additional surgeries, as stated in our bullets; and, (2) we are concerned that the additional survival data will still be confounded by the imbalance in histologies between the arms, also stated in our bullets. We underscore that we wish to have another meeting with the applicant before considering a submission.

Statistical Comments:

(1). As specified in the protocol, the Cox model approach is an exploratory analysis.
(2). The tests for treatment effect (not stratified by Country) using AGE either as a continuous variable or dichotomized variable in the multivariate Cox model (with AGE, KPS, and GBM) are NOT statistically significant (p-values: 0.162 for continuous AGE; 0.082 for dichotomized AGE). SAS output is attached.

(3). According to our analysis, neither dichotomized age nor continuous age can hold the PH assumption ($p<0.05$). Please submit your SAS output for us to review.

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence	Limits
TRTGRP	1	-0.21046	0.15059	1.9531	0.1623	0.810	0.603	1.088
AGE	1	0.03541	0.00992	12.7401	0.0004	1.036	1.016	1.056
KPS	1	-0.58607	0.16320	12.8958	0.0003	0.557	0.404	0.766
GBM	1	0.29090	0.26082	1.2439	0.2647	1.338	0.802	2.230

Analysis of Maximum Likelihood Estimates

Variable	Variable Label
TRTGRP	Randomization Group
AGE	Age (years)
KPS	
GBM	Patient with Glioblasta Multiforme

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/s/

Paul Zimmerman
6/25/02 09:57:44 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

SNDA 20-637\S-016

Guilford Pharmaceuticals Inc.
Attention: Louise Peltier
Senior Director, Regulatory Affairs
6611 Tributary Street
Baltimore, MD 21224

Dear Ms. Peltier:

We received your March 19, 2002 correspondence on March 20, 2002 requesting an end of review conference and copies of all discipline reviews.

Per your request, a meeting to review the issues leading to nonapproval will be scheduled, and will include Dr. Robert Temple if possible. We respectfully decline to forward our discipline reviews, which are not consensus documents. We refer you to the points outlined in our letter of March 19, 2002 for citation of the issues that prevented approval.

If you need any additional information or have any questions regarding this matter, please contact Paul Zimmerman at 301-594-5775.

Sincerely,

/S/

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
4/4/02 11:36:59 AM

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise Peltier	From: Debbie Vause for P. Zimmerman
Fax: 410-631-6884	Fax: 301-594-0499
Phone: 410-631-6300	Phone: 301-594-5724
Pages, including cover sheet: 1	Date: August 14, 2001

Re: NDA 20-637 / Gliadel Wafer / Facsimile date 8/2/01 & Transmission Sheet Date 8/3/01

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

● Dear Ms. Peltier:

In the facsimile submission dated 8-2-01 regarding randomization, you stated "The randomization algorithm was accomplished with each center in a given country." Was the randomization stratified by CENTER or COUNTRY?

In the same facsimile you also stated "...using a randomization code (block size of four) independently of randomization code of any other study center. Does this mean that a specific block only be used by a center? Please clarify this statement.

Please review the attached questions and provide a response by COB on Wednesday, August 15, 2001.

Thank you,

Debbie Vause

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/s/

Debra Vause
8/14/01 01:36:42 PM
CSO